UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/808,382	03/14/2001	Benjamin Eithan Reubinoff	14418	1139

7590 06/01/2006

SCULLY, SCOTT, MURPHY & PRESSER
400 Garden City Plaza
Garden City, NY 11530

EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/808,382	REUBINOFF ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39,44-46,51,56-58,60,61,63,64,67,68,86,94 and 100-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,44-46,51,56-58,60,61,63,64,67,68,86,94 and 100-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/23/06 has been entered.

Applicants' Amendment and Remarks filed 3/23/06 have been entered. Claims 39, 45, 46, 51, 56-58, 60, 61, 63, 64, 67, 68, 94 are amended; claims 100-104 are newly added; claims 39, 44-46, 51, 56-58, 60, 61, 63, 64, 67, 68, 86, 94, 100-104 are pending and under current examination.

The Colman Declaration, filed 3/23/06, has been considered.

Claim Rejections - 35 USC § 112

The prior rejection of claims 39-46, 51, 56-58, 60-68, 86, 88-99, under 112, 1st paragraph, for written description, is withdrawn. The claims are now amended to require the expression of NCAM, nestin, vimentin and Pax-6, and thus, provide description for the neural progenitor cells.

The prior rejection of claims 39-46, 51, 56-58, 60-68, 86, 88-99, under 112, 1st paragraph, for enablement, is withdrawn. The claims are now enabled because the claims have been amended such that the phrase "controlled differentiating condition" is no longer claimed.

Claim Rejections - 35 USC § 102

The prior rejection of claims 39-46, as being anticipated by Shamblott *et al.* is withdrawn, because the claims, as newly amended, now require specific method steps that are not recited in the cited art of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* in view of Brustle. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/21/05.

Applicants' Arguments. Applicants argue that because Thomson teach that that hES cells *in vitro* differentiate into trophoblast and endoderm lineages, but that they do not teach the generation of a lineage to relevant to neural cell types (ectoderm), and that they only teach the broader developmental potential of hES cells *in vivo* (via teratoma formation), and the difference between the *in vitro* and *in vivo* results, one of skilled in the art would conclude that it would be difficult to direct differentiation of hES cells towards a neural lineage *in vitro*. Applicants argue that Thomson does not provide motivation for those of skilled in the art to culture hES cells *in vitro* to generate neural progenitor cells that could be further differentiated into neuronal cells, into oligodendrocytes or into astrocytes. See page 16 of the Response. The Colman Declaration reiterates Applicants' arguments, namely in stating that Thomson *et al.* do not show *in vitro* differentiation of hES cells into ectoderm lineages (p. 3, #11).

Response to Arguments. Applicants' arguments are considered, but not found to be persuasive. In particular, Applicants' arguments are not analogous with the claimed invention. The claimed invention is directed to the directed differentiation of hES cells to neural progenitor cells, under specific conditions, with specific media

and growth factors. Thomson *et al.* teach that in spontaneously differentiating conditions, hES cells did not form ectoderm lineage cells. However, they do show that the hES cells have the capability to do so, as shown by the formation of teratoma *in vivo* results, under appropriate conditions. Thus, although spontaneous differentiation does not result in ectoderm formation, this does not mean that hES cells cannot form ectoderm lineage cells. This is clearly show by Thomson's results showing ectodermal cells in teratomas formed when hES cells are injected into SCID mice.

Applicants' Arguments. Applicants argue that Brustle is directed to culturing mouse ES cells, and that it was evident, even at the time of priority of the instant case, that the differences between mouse and human ES cells were so substantial that those skilled in the art would not have had a reasonable expectation of success in producing human NPCs, and to further differentiate such human NPCS, by simply applying the conditions developed using mES cells, as taught by Brustle. Page 17 of the Response. Applicants argue that the manner in which the cells are maintained in culture will vastly affect the outcome upon induction of differentiation, because mES cells are cultured and behave differently from hES cells. See page 17 of the Response. Applicants argue that Brustle only show the derivation of glial precursors, which can differentiate into oligodendrocytes and astrocytes, but do not show neuron formation. Applicants argue that the methods, as taught by Brustle do not anticipate or suggest the instant invention, because they do not teach production of neural progenitor cells that can produce oligodendrocytes, astrocytes and neuronal cells. Therefore, Applicants conclude that those skilled in the art not only would not have had a reasonable expectation of success in applying the conditions, as taught by Brustle, to produce the multipotent human neural progenitor cells, as presently claimed. See page 18, 1st ¶ of the Response. See also, p. 6, #19 of the Declaration.

Response to Arguments. Applicants' arguments are fully considered, but not persuasive. The claims, as now amended, require a serum free medium, which include EGF, bFGF, in order to produce neural progenitor cells (claim 39). Brustle provides these specific conditions. See p. 754, 2nd column which states that FGF2 is also known as basic fibroblast growth factor, and page 756, #7, 1st column. Thus, although they do not specifically teach that neuronal cells are formed, if one were to use Brustle's conditions (which are the same as what is instantly claimed), one would necessarily arrive at the claimed invention, which is the formation of neural progenitor cells that are capable of further differentiation into neurons, oligodendrocytes, and astrocytes. Simply put, because there are no differences between the culture conditions of Brustle, and the instantly claimed invention, one of skill in the art would necessarily produce the same cells, with the same expression markers.

Colman Declaration. Applicants submit the Colman Declaration as support for these arguments, namely in that the differences between hES and mES cells were known to be significant in 2000, such that one of skill in the art would not be able to readily extrapolate the results achieved with mES cells to hES cells. In particular, the Declaration states that the art noted in 1998, that there are differences between mES and hES cells with regard to the culture conditions of the cells in the presence of LIF. Particularly, that the presence of LIF could not prevent the differentiation of hES cells, and in contrast, prevented differentiation of mES cells. See page 2, #8 of the Declaration. The Declaration further states that, in 1998, the art recognized that LIF is one of a number of cytokines that activate the JAK/STAT signaling pathway, and therefore, it was believed at the time that the JAK/STAT signaling pathway was in some way deficient in hES cells. Ginis *et al.* is post-filing art that shows that gp130 and the LIF receptor, which make up the LIF receptor complex, were missing in many hES cells lines. See page 3, 1st ¶. The Declaration further states that before 2000, the JAK/STAT signaling pathway was

implicated in many aspects of development, including division, survival and differentiation of embryonic central nervous system cells (citing Cattaneo *et al*), and that LIF has been shown to be necessary for the development and survival of oligodendrocytes in an *in vitro* model. See p. 3, #9. The Declaration concludes that given the understanding that hES cells, but not mES cells, lack a component of the JAK/STAT pathway, and the importance of this pathway in the development of neural cells, there would have been no reasonable expectation of success, prior to March 14, 2000, that hES cells would behave in the same way as mES cells, when subjected to neural differentiation protocols developed using mES cells. See page 3, #10. The Declaration cites Svendsen and Smith (1999) as evidence that there are differences in the proliferation capacity between human pluripotent stem cells (HPCs) and mES cells, in particular, that HPCs are more difficult to expand, and it is uncertain whether the human cells use the same intracellular signaling pathways as mES cells to sustain the self-renewal cycle. Applicants further cite Xu *et al.*, who teach the growth factor BMP4, to induce differentiation of hES cells to trophoblast, and show that although hES cells can form trophoblast, mES cells cannot, thus underscoring the differences between the two cells (see p. 4, #12-15).

Response to Declaration. The Colman Declaration, and all supporting references have been fully considered, but is not persuasive. Firstly, Xu relates to *in vivo* studies, teaching that mouse ES cells yield very low trophoblast cells, not that mES cells are unable to form any trophoblast cells. This article cites Beddington *et al.* (**Development**, 105:733-737 (1989)), as evidence for this, Beddington *et al.* teaches that injection of ES cells into host blastocysts, and the testing of their developmental potential in the developing embryo. Beddington *et al.* is not within the scope of the instant rejection, as Beddington is directed to *in vivo*. The instant claims are directed to *in vitro* differentiation of hES cells to human neuronal progenitor cells. Beddington *et al.* does not compare between *in*

vitro differentiation of mouse ES cells in the same conditions as human ES cells, and comparison of resultant cells.

Furthermore, although it is recognized that there are different conditions, when culturing mES cells and hES cells, with regard to the presence of LIF to inhibit differentiation, there is no evidence in the art of record, state of the art at the time of filing, or Applicants' arguments, that show that hES cells cannot form cells of neuronal lineages due to the gp130 deficiency (which was determined post-filing). Cattaneo *et al.* (cited by Applicants) clearly teach that both receptor-protein tyrosine kinases, and cytokine receptors (JAK/STAT) are involved in neuronal and glial differentiation (see page 365, 1st column, 1st paragraph). The JAK/STAT pathway is found to be diverse, with various members of JAKs and STATs (see page 365, 2nd column). Furthermore, gp130, as taught by Niwa *et al.* (cited by Applicants) interacts with STAT3 (see Abstract). Thus, although hES cells do not have the gp130/STAT3 interaction, Declarant has provided no evidence that the art, at the time of filing, regarded hES cells incapable of forming cells of neuronal lineages. On the other hand, this evidence is provided by Thomson *et al.*, who clearly show that the cells have the capability to form ectodermal cells, given appropriate conditions. Teratoma formation is routinely used in the art to show the differentiation potential of an ES cell. Since Thomson *et al.* showed hES cells form ectodermal cells in a teratoma, and ectodermal cells give rise to neural progenitor cells, as taught by Brustle, the artisan would have had the teachings, suggestion and motivation to apply the differentiation method, taught by Brustle, which target the differentiation of mES cells, which form ectodermal cells in a teratoma, using culture conditions identical to those claimed. One of skill in the art would have had a reasonable expectation of success, because hES cells, as mES cells, formed ectodermal cells in a teratoma.

In short, one of skill in the art, at the time of filing, would have recognized differences between hES cells and mES cells, particularly with regard to culturing

the cells in presence of LIF. However, one of skill in the art would have also recognized that hES cells had the capacity to differentiate into cell types from all three embryonic germ layers, including cells of neuronal lineage (as taught by Thomson). One of skill in the art would recognize that protocol existed to direct differentiation of mouse ES cells to a particular cell type (such as neuronal cells) (as taught by Brustle). One of skill in the art would be motivated to use this protocol on human ES cells, with a reasonable expectation of success. Accordingly, the prior rejection is maintained.

Thomson teach embryonic stem cell lines derived from human blastocysts. They teach that the cells are isolated from human embryos which were cultured to blastocyst stage and the inner cell masses isolated and cultured (see p. 1145, 2nd column). They teach that the cells expressed markers for human pluripotent stem cells (p. 1145, col. 3, last paragraph), they teach that the cells had a normal karyotype (p. 1145, 2nd column) and produced teratomas when injected into SCID mice (p. 1146, 1st column). They teach culturing the hES cells on irradiated mouse embryonic fibroblasts (page 1147, #6) and that these cells were able to proliferate undifferentiated past 6 months (p. 1145, col. 2-3, bridging sentence). They do not teach methods of producing human progenitor cells by culturing the cells in serum free medium supplemented with EGF and bFGF.

However, prior to the time of filing, Brustle teach methods of inducing differentiation of mouse ES cells to glial precursors, a somatic progenitor cell, by culturing mouse ES cells in the presence of FGF2 and PDGF-AA in serum free media and on polyornithine coated dishes (p. 754, 2nd col. 2, lines 1-7; p. 756, 1st col., lines 14-27). The withdrawal of growth factors caused the progenitor/stem cells to differentiate into oligodendrocytes (p. 754, 2nd col., lines 13-15, p. 756, col. 1, lines 30-31).

Claims 58-58, 86 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* in view of Brustle *et al.* as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Stemple *et al.* This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. It is maintained that, at the time of the instant invention, it would have been obvious to the ordinary artisan to culture human ES cells, as taught by Thomson, in serum free media in the presence of FGF2 and PDGF-AA on polyornithine to form neural precursors, as taught by Brustle, but growing in the precursors in a media comprising retinoic acid and growth on poly-D-lysine and laminin coated plates to induce neuronal growth, as taught by Stemple, for drug discovery and/or transplantation therapies. The methods will necessarily result in neural progenitor cells that express the particular markers claimed, because the claims require the same growth factors and medium. The cited prior art provides sufficient suggestion, teaching and motivation to arrive at the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 61, 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson in view of Brustle in view of Stemple, as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Ben-Hur. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. Thus, it is maintained that it would have been obvious for one of ordinary skill in the art, at the time of filing, to culture

the human ES cells, as taught by Thomson in serum free media in the presence of FGF and PDGF-AA, on polyornithine to form glial precursors and then, in the absence of growth factors, to form predominantly oligodendrocytes and astrocytes, as taught by Brustle, but growing the precursors on poly-D-lysine and fibronectin coated plates, in order to enhance the presence of neurons in the differentiated cells and in the presence of EGF to enhance neuron differentiation, followed by culture with EGF and T3 to produce a culture of neuronal cells, oligodendrocytes, and glia cells for drug discovery and/or transplantation therapies, as taught by Ben-Hur, with a reasonable expectation of success.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 68 and 94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson and Brustle as applied to claims 39, 44-46, 51, 60, 63, 64, 67, 100-104 above, and further in view of Ben-Hur. This rejection is maintained for reasons of record, advanced in the prior Office action, mailed 11/21/05.

Applicants' present no specific arguments with regard to this rejection. Applicants' arguments are addressed above. Accordingly, it is maintained that, at the time of the claimed invention, it would have been obvious for one of ordinary skill in the art, to produce oligodendrocytes by culturing the human ES cells, as taught by Thomson in DMEM/F12 media, in the presence of FGF2 and EGF to form glial precursors, as taught by Brustle, and to further culture the glia cells in the presence of B27, FGF2 and EGF, as taught by Ben-Hur, in combinations to provide oligodendrocytes for drug discovery and/or transplantation. The cited art provides sufficient suggestion, teaching and motivation to achieve the claimed invention.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tnt
Thaian N. Ton
Patent Examiner
Group 1632

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630